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INTELLECTUAL PROPERTY **INDIA**
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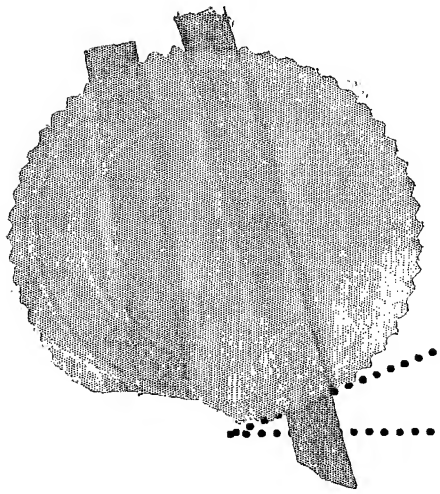
सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

## THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 23/12/2003 in respect of Patent Application No.1304/MUM/2003 of SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI- KURLA ROAD, ANDHERI (E), MUMBAI – 400 059, MAHARASHTRA, INDIA, AN INDIAN COMPANY.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 23rd day of February 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA**

**AN INDIAN COMPANY**

hereby declare -

(i) that we are in possession of an invention titled **"STABLE ORAL COMPOSITION"**.

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

**(1) Dr. Khapra Pankaj;** and **(2) Dr Dharmadhikari, Nitin Bhalachandra;** both of SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE LIMITED, Bombay College of Pharmacy Building, 2nd Floor, C.S.T. Road, Kalina, Mumbai 400098, Maharashtra, INDIA; both Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

**Dr. RATNESH SHRIVASTAVA,**
**INTELLECTUAL PROPERTY CELL,**
**SUN PHARMACEUTICAL INDUSTRIES LTD,**
**ACME PLAZA, ANDHERI-KURLA ROAD,**
**ANDHERI (E), MUMBAI-400 059, INDIA,**
**TELEPHONE NO-28397632, FACSIMILE NO- 28212010.**

ORIGINAL

1304

97/mum-WTO/2003

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1304 मुंबई MUM 2003

23/12/03

23 DEC 2003

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 23rd day of December, 2003.

(Signatures) 1. P. Khapra

**Dr. Khapra, Pankaj**

2. N. B. Dharmadhikari

**Dr. Dharmadhikari, Nitin Bhalachandra**

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

1) Provisional specification (3 copies)
2) Fee Rs. 3000 by cheque bearing No. 436132 dated 15/12/2003 on ICICI Bank Limited.

We request that a patent may be granted to us for the said invention

Dated this 23rd day of December, 2003.

(Signature) .....

**DILIP SHANGHVI**
**CHAIRMAN AND MANAGING DIRECTOR**
**SUN PHARMACEUTICAL INDUSTRIES LTD.**

To

The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

**FORM 2**

**THE PATENTS ACT, 1970**
(39 OF 1970)

**PROVISIONAL SPECIFICATION**
(See section 10; rule 13)

ORIGINAL

# STABLE ORAL COMPOSITION

**SUN PHARMACEUTICAL INDUSTRIES LTD.**

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.



**The following specification describes the nature of this invention.**

# STABLE ORAL COMPOSITION

The present invention relates to a solid oral pharmaceutical composition. More specifically this invention relates to stable oral compositions of descarbonylethoxyloratadine.

## BACKGROUND OF THE INVENTION

Descarbonylethoxyloratadine, also called desloratadine, is chemically known as 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine. Desloratadine, a metabolic derivative of loratadine, is a long-acting tricyclic histamine antagonist with selective $H_1$-receptor histamine antagonist activity. Descarbonylethoxyloratadine is indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients 12 years of age and older. It is also indicated for the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria, 12 years of age and older.

United States Patent Number 6,100,274 claims a stable pharmaceutical composition of desloratadine comprising a desloratadine-protective amount of a pharmaceutically acceptable basic salt and at least one pharmaceutically acceptable disintegrant. The patent mentions that acidic excipients discolor and decompose desloratadine. Desloratadine compositions were found to discolor when stored at 75% relative humidity ("RH") and a temperature of 40° C, alone or in combination with various excipients. This color instability in the active ingredient was attributed to a very minute amount of degradation product, the N-formyl impurity, which is formed due to the presence of a wide variety of excipients commonly used in oral formulations - especially tablet formulations. The unsuitable excipients include acidic excipients including, but not limited to, stearic acid, povidone and crospovidone, and other acidic excipients having a pH in water less than 7, preferably in the range of about 3 to 5, as well as excipients such as lactose, lactose monohydrate, sodium benzoate, and the like. The patent teaches the use of calcium, magnesium and aluminum salts of carbonates, phosphates, silicates and sulfates, or mixtures thereof. However, the patent does not teach any other means of stabilizing desloratadine.

United States Patent Application Number 20020123504A1 relates to stable pharmaceutical compositions of desloratadine formulated to avoid the incompatibility between desloratadine and reactive excipients such as lactose and other mono- and di-saccharides. Disclosed compositions include lactose-free, non-hygroscopic and anhydrous stable pharmaceutical

compositions of desloratadine. The patent application teaches that stable desloratadine can be obtained by using anhydrous process and excipients, such that the unbound water that may be present in the formulation is insufficient to initiate and/or accelerate any reaction of desloratadine with reactive excipients. Other means of stabilization taught by the patent application include coating of desloratadine particles to avoid contact with reactive excipients, or using large particles of desloratadine, so that surface area of contact with the reactive excipients is reduced. However, the methods suggested in this application either provide solutions that involve avoiding conventional formulation procedures such as wet granulation, or suggest other means that may affect bioavailability of the formulation, for example, coating or using large particles.

It is an object of the present invention to provide a stable pharmaceutical composition of desloratadine.

It is another object of the present invention to find novel means for stabilizing desloratadine compositions.

It is yet another object of the present invention to prevent or decrease the formation of N-formyl impurity in desloratadine composition, using novel means of stabilization.

It is still another object of the present invention to provide a pharmaceutical composition for desloratadine, which composition is stable in the presence of reactive excipients.

We have surprisingly found that pharmaceutical compositions comprising desloratadine can be stabilized using a stabilizer selected from an antioxidant, a pharmaceutically acceptable organic compound that provides an alkaline pH, an alkali metal salt or mixtures thereof. Hence, the invention lies in the use of a stabilizer, which stabilizer provides stability, while providing the freedom to use conventional excipients and processes.

Accordingly, the present invention provides a stable oral composition comprising a pharmaceutically acceptable amount of desloratadine and a desloratadine-protective amount of a stabilizer selected from an antioxidant, a pharmaceutically acceptable organic compound that provides an alkaline pH, an alkali metal salt, or mixtures thereof.

The antioxidants used in the present invention may be selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole, DL-alpha-tocopherol, propyl gallate, octyl gallate, ethylenediaminetetraacetate, ascorbyl palmitate, acetyl cysteine, ascorbic acid,

sodium ascorbate, fumaric acid, lecithin and the like and mixtures thereof. The pharmaceutically acceptable organic compound used in the present invention to provide an alkaline pH may be selected from the group consisting of primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), monosodium glutamate, polacrillin sodium, sodium alginate, and mixtures thereof. Alkali-metal salts that may be preferably used include sodium and potassium salts of carbonates, phosphates, silicates, sulfates, citrates and the like. The stabilizer is used in an amount sufficient to protect the desloratadine so as to provide a composition having less than 1% by weight of N-formyl desloratadine.

The pharmaceutical composition of the present invention may also further comprise of inert pharmaceutically acceptable excipients such as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet disintegration agents or encapsulating materials.

The disintegrants used in the present invention may be selected from the group consisting of microcrystalline cellulose, starch, e.g., pregelatinized starch and corn starch, croscarmellose sodium and confectioner's sugar (a mixture of at least 95% by weight sucrose and corn starch that has been ground to a fine powder).

The binders used in the present invention may be selected from the group consisting of starch, gelatin, dextrin, maltodextrin, natural and synthetic gums like acacia, alginic acid, sodium alginate, guar gum, extract of Irish moss, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, veegum, arabogalactan and the like and mixtures thereof.

The lubricants used in the present invention may be selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, polyethylene glycol and the like and mixtures thereof.

The typical glidants that may be included in the present invention include colloidal silicon dioxide, talc and the like.

Examples of wicking agents that may be used in the present invention include colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, niacinamide, sodium lauryl sulfate, m-pyrol, vinylpyrrolidone polymers such as povidone, or crosslinked polyvinylpyrrolidone such as crospovidone; cellulose and cellulose derivatives such as

microcrystalline cellulose, methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropyl cellulose, carboxyalkyl celluloses or crosslinked carboxyalkylcelluloses and their alkali salts; sodium starch glycolate, starch and starch derivatives, ion-exchange resins and the like and mixtures thereof.

The present invention may also include various other pharmaceutically acceptable excipients, sweetening agents, wetting agents, flavoring agents, coloring agents and other such excipients.

The term "pharmaceutical composition" as used herein includes solid oral dosage forms such as pellets, beads, granules and the like, which may be encapsulated or compressed into tablets. The pellets, beads, granules in turn may be prepared by conventional methods known to a person skilled in the art. The compressed tablets may optionally be coated with film-coat.

The pharmaceutical composition of the present invention may be prepared by the conventional process of wet granulation, dry granulation or direct compression. In wet granulation, the drug along with the stabilizer and various excipients is mixed, granulated, followed by screening and drying of the damp mass. The dried mass may be screened, lubricated and compressed. Dry granulation can be done by two processes: (1) slugging, which involves mixing the drug with the stabilizer and the excipients, slugging, dry screening, lubrication and compression, and (2) roller compaction process. Direct compression involves compressing tablets directly from the powdered material of the drug, the stabilizer and the excipients.

The examples that follow do not limit the scope of the invention and are merely used as illustrations.

**Example 1**

The oral pharmaceutical composition of the present invention was obtained as per the method given in Table 1 below.

**Table 1**

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | Percent weight by weight |
| | | |
| Desloratadine | 5.0 | 5.0 |
| Butylated hydroxytoluene | 0.1 | 0.1 |
| Meglumine | 1.0 ( in water) | 1.0 |
| Microcrystalline cellulose (Avicel PH 101) | 30.0 | 30.0 |
| Starch 1500 | 15.0 | 15.0 |
| Corn Starch Purity 21A | 36.9 | 36.9 |
| Microcrystalline cellulose (Avicel PH 102) | 10.0 | 10.0 |
| Talc | 2.0 | 2.0 |
| **Average weight** | **100.0** | **100.0** |

The butylated hydroxytoluene was dissolved in isopropyl alcohol. The desloratadine was granulated with the butylated hydroxytoluene solution and the granules were then dried (Stage I granules). Microcrystalline cellulose (Avicel PH 101), corn starch Purity 21 A and starch 1500 were mixed and granulated using meglumine solution in water. These granules were dried (Stage II granules). The Stage I granules and Stage II granules were mixed and lubricated with Avicel PH 102 and talc and compressed into tablets. The tablets were coated with aqueous coating dispersion.

The tablets thus obtained were subjected to dissolution testing using United States Pharmacopoeia type II dissolution apparatus at 50 rpm at 37 ± 0.5°C. The dissolution medium used was 500 ml of 0.1N HCl. The results of the dissolution test are mentioned in Table 2 below.

**Table 2**

| Time (mins) | Percent drug released |
|---|---|
| 0 | 0 |
| 10 | 84 |
| 20 | 89 |
| 30 | 92 |
| 45 | 97 |

**Example 2**

The oral pharmaceutical composition was obtained as per the method given in Table 3 below.

**Table 3**

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | Percent weight by weight |
| Desloratadine | 5.0 | 5.0 |
| Meglumine | 1.0 ( in water) | 1.0 |
| Microcrystalline cellulose (Avicel PH 101) | 30.0 | 30.0 |
| Starch 1500 | 15.0 | 15.0 |
| Corn Starch Purity 21A | 37.0 | 37.0 |
| Microcrystalline cellulose (Avicel PH 102) | 10.0 | 10.0 |
| Talc | 2.0 | 2.0 |
| **Average weight** | **100.0** | **100.0** |

Desloratadine, Avicel PH 101, Corn Starch Purity 21 A and Starch 1500 were mixed. The dry mixture was granulated with Meglumine solution. The granules were dried, lubricated with Avicel PH 102 and Talc and compressed into tablets. The tablets were coated with aqueous coating dispersion.

**Example 3**

The oral pharmaceutical compositions were obtained as per the method given in Table 4 and 5 below.

**Table 4**

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | Percent weight by weight |
| Desloratadine | 5.0 | 5.0 |
| Butylated hydroxytoluene | 0.1 | 0.1 |
| Microcrystalline cellulose (Avicel PH 101) | 72.15 | 72.15 |
| Starch 1500 | 15.0 | 15.0 |
| Sodium starch glycolate | 4.0 | 4.0 |
| Colloidal silicon dioxide | 1.5 | 1.5 |
| Talc | 2.0 | 2.0 |
| Magnesium stearate | 0.25 | 0.25 |
| **Average weight** | **100.0** | **100.0** |

The butylated hydroxytoluene was dissolved in isopropyl alcohol. The desloratadine was granulated with the butylated hydroxytoluene solution. The granules were dried and mixed with Avicel PH 112, Starch 1500, Sodium Starch Glycolate, Colloidal Silicon Dioxide, talc and Magnesium Stearate and compressed into tablets. The tablets were coated with aqueous coating dispersion.

**Table 5**

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | Percent weight by weight |
| Desloratadine | 5.0 | 5.0 |
| Butylated hydroxytoluene | 0.1 | 0.1 |
| Microcrystalline cellulose (Avicel PH 101) | 30.0 | 30.0 |
| Starch 1500 | 15.0 | 15.0 |
| Corn Starch Purity 21A | 37.9 | 37.9 |
| Microcrystalline cellulose (Avicel PH 102) | 10.0 | 10.0 |
| Talc | 2.0 | 2.0 |
| **Average weight** | **100.0** | **100.0** |

The butylated hydroxytoluene was dissolved in isopropyl alcohol. The desloratadine was granulated with the butylated hydroxytoluene solution and the granules were dried. Avicel PH 101, Corn Starch Purity 21 A and Starch 1500 were mixed and granulated using water. The granules were then dried. These granules were mixed with the desloratadine granules, lubricated with Avicel PH 102 and Talc and compressed into tablets. The tablets were coated with aqueous coating dispersion.

**Comparative example 1**

Oral pharmaceutical composition of desloratadine comprising no stabilizer was prepared as per Table 6 below.

**Table 6**

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | Percent weight by weight |
| Desloratadine | 5.0 | 5.0 |
| Microcrystalline cellulose (Avicel PH 101) | 30.0 | 30.0 |
| Starch 1500 | 15.0 | 15.0 |
| Corn Starch Purity 21A | 38.0 | 38.0 |
| Microcrystalline cellulose (Avicel PH 102) | 10.0 | 10.0 |
| Talc | 2.0 | 2.0 |
| **Average weight** | **100.0** | **100.0** |

Desloratadine, Avicel PH 101, Corn Starch Purity 21 A and Starch 1500 were mixed and granulated using water. The granules were lubricated with Avicel PH 102 and Talc and compressed into tablets. The tablets were coated with aqueous coating dispersion.

The tablets of examples 1, 2 and 3 were found to stable, physically and chemically, as compared to the tablets of comparative example 1.

Dated this 23rd day of December, 2003

**DILIP SHANGHVI,**
**CHAIRMAN AND MANAGING DIRECTOR,**
**SUN PHARMACEUTICAL INDUSTRIES LIMITED.**